# CLINICAL PRACTICE GUIDELINE: CANCER OF THE LUNG (Primary or Metastatic, Suspected or Diagnosed) (2A)

## SYSTEMATIC REVIEW FOR IMAGING OF CANCER OF THE LUNG

## CPG 2A Abstract (Updated August 2019)

Lung cancer is the most common cancer affecting both men and women in the United States, accounting for an estimated 228,150 new cases in 2019, representing 12.9% of all new cancer cases. Lung cancer is the leading cause of death from cancer in men and women, accounting for an estimated 142,670 deaths in 2019, comprising approximately 23.5% of all cancer deaths in the United States. Although improved, the 5-year survival rate for lung cancer patients remains below 20% (National Cancer Institute: Surveillance, End Results and Epidemiology Program SEER Stat Fact Sheets: Lung and Bronchus Cancer (SEER, 2019).

A concerning aspect of lung cancer is that upon diagnosis, the tumor is often deemed non-operable. Although serial CT scanning was found to be an effective screening tool among the smoking population (De Koning et al., 2018; Moyer, 2014), this was not evident in the general population. Furthermore, annual CXR and serial sputum cytology evaluations among the general population were not capable of reliably identifying patients with early disease.

The presenting signs ans of lung cancer are frequently indicative of tumor stage, especially when symptoms are pleural-based or extra-thoracic in nature. Symptoms include cough, hemoptysis, chest or shoulder pain, dyspnea, hoarseness, weight loss, anorexia, fever, weakness, and bone pain (Birring & Peake, 2005). A high index of suspicion on the part of clinicians is paramount as this may lead to earlier diagnosis and the potential for a more favorable prognosis.

Once a diagnosis of lung cancer is suspected based on chest radiography (CXR), further evaluation involves advanced imaging such as computed tomography (CT), positron emission tomography (PET) with or without CT scanning, bone scintigraphy, and magnetic resonance (MR) imaging. This information can then be used to stratify patients for treatment (Murgu, 2015). If tissue is desired for histology, current options include CT-guided transthoracic needle biopsy, direct fiberoptic bronchoscopy, endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA), and open or thoracoscopic surgery.

**Multiple factors affect the decision-making process when determining the appropriate imaging study for a specific clinical situation. These factors include cost (both initial and 'downstream'), availability, patient preference and expectations, radiation exposure concerns, prior imaging results, and presence of contraindications for a specific modality. Further, such factors are not always quantifiable and frequently vary across clinical settings. Panelists review available literature to recommend appropriate imaging studies for specific clinical scenarios but acknowledge that these other variables impact the decision-making process and**

**are not necessarily addressed by published literature. In the recommendation justifications, these issues would be part of the consideration, especially when the resulting "grade" is judged to be "Consensus" rather than based upon strong clinical evidence.**

**Database sources:** ResearchGate, PubMed, Google Scholar, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews.

**Search Strategy:** For this annual review, a systematic search and a thorough review of the medical literature which focused on lung cancer in adults and appropriate diagnostic imaging techniques, published in the last five year through August 2019, was conducted. The advanced search option in PubMed/Medline was used, incorporating the search strategy utilizing Population, Intervention, Comparator, Outcome (PICO) framework.

**Keywords:** The following keywords (using MeSH and full-text search strings) were used individually or in combination with one another in different permutations and/or combinations using Boolean Operators: lung cancer, solitary pulmonary nodule, surveillance, screening, staging, bone metastasis, brain metastasis, chest x-ray, chest CT, PET-CT of the thorax, Computed tomography lung, contrast-enhanced CT, MR imaging, Endobronchial Ultrasound-Guided Fine-Needle Aspiration (EBUS), small cell lung cancer, non-small cell lung cancer, accuracy, sensitivity and specificity.

**Methods:** A total of 6982 articles resulted from the general lung cancer imaging topic search. References of relevant articles were scanned for potentially missing studies. Titles and abstracts were scanned, and then full articles were reviewed. The articles were evaluated and considered from the following groups: evaluation of clinical predictors of lung cancer using chest x-ray in adults (140 articles), computed tomography (CT) imaging of the chest (398 articles), staging of lung cancer using PET-CT (39 articles), Endobronchial Ultrasound-Guided Fine-Needle Aspiration (EBUS) or CT- guided transthoracic needle biopsy (207 articles), surveillance and metastasis (136 articles) and the evaluation of solitary pulmonary nodules comparing PET-CT/CT (77 articles). Some articles were considered for more than one group. Finally, these articles were evaluated, based, in part, upon study design, sample size, and public availability. They were further reviewed to see if they answer the respective PICO questions.

Based on 2019 literature review the following changes have been made to the Clinical Practice Guideline: 1) Major revisions and updates have been made to the PICO's that address staging and evaluation of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). 2) Two new PICO's have been created: One for diagnostic evaluation of solitary pulmonary nodule(s) and second for screening for lung cancer (patient population and preferred imaging modality have been studied).

## Clinical Focus Questions

**PICO #1:** What clinical predictors warrant initial chest XR in adults with risk factors for lung cancer for optimal diagnostic assessment?

**PICO #2:** In adults with chest XR findings suggestive of malignancy, is computed tomography (CT) imaging of the chest warranted for further diagnostic assessment?

**PICO #3:** In adults with chest lesions requiring biopsy, what clinical parameters favor endobronchial ultrasound guided (EBUS) vs CT-guided transthoracic needle biopsy for optimal diagnostic accuracy?

**PICO #4:** In adults with cancer of the lung, should PET-CT imaging be performed to stage the tumor compared to other imaging for optimal patient management?

**PICO #5**: In adults with lung cancer where bone metastases are suspected, which imaging modality is preferred for optimal diagnostic accuracy?

**PICO #6:** In adults with non-small cell lung cancer (NSCLC), when is imaging to identify brain metastases warranted for optimal patient management?

**PICO #7:** In adults with non-small cell lung cancer (NSCLC), who have had curative treatment, which imaging modality should be used for surveillance?

**PICO #8:** In adults with limited stage small cell lung cancer (SCLC), who have had definitive treatment, should CT imaging be performed as part of surveillance monitoring for optimal patient management?

**PICO #9:** In which adult populations is lung cancer screening indicated and which imaging modality is preferred for optimal management/assessment?

**PICO #10:** In adults found to have a Solitary Pulmonary Nodule(s) (SPNs), should PET-CT or CT be performed to differentiate between benign and malignant lesions?

**PICO #1:** What clinical predictors warrant initial chest XR in adults with risk factors for lung cancer for optimal diagnostic assessment?

| SEMPI Grading QOE – Table 2A.1a – Summary of Findings | | | | | | |
|---|---|---|---|---|---|---|
| **PICO #1:** What clinical predictors warrant initial chest XR in adults with risk factors for lung cancer for optimal diagnostic assessment? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Okoli et al., 2018 Is symptom-based diagnosis of lung cancer possible? A systematic review and meta-analysis of symptomatic lung cancer prior to diagnosis for comparison with real-time data from routine general practice | Meta-analysis | 13 studies | No Comparison<br><br>Identifying pre-diagnostic features of lung cancer | Diagnostic odds ratio for lung cancer:<br>Hemoptysis = 6.39 (3.32–12.28)<br>Dyspnea = 2.73 (1.54–4.85)<br>Cough = 2.64 (1.24–5.64)<br>Chest pain = 2.02 (0.88–4.60)<br><br>Up to 20% of all initial chest X-rays from patients subsequently diagnosed with lung cancer are negative | To avoid false negative X-ray results in patients subsequently diagnosed with lung cancer, symptomatology and risk factors should be considered to improve diagnostic assessment | Moderate |
| Neal et al., 2017 Immediate chest X-ray for patients at risk of lung cancer presenting in primary care: randomised controlled feasibility trial | Randomized clinical trial | Adult patients > 60 (smokers or ex-smokers with ≥ 10 packs/year) – 255 patients | Urgent XR versus normal care for patients presenting with altered cough, increased dyspnea or wheezing | XR was normal in 70.9% and 50% in the urgent XR and normal care groups respectively.<br><br>XR detected cancer in 1.2% of the study participants<br>Out of all study population, 4 patients had a suspicious XR. 3 of them were confirmed to have cancer | Chest x-ray findings are often normal in symptomatic patients, later diagnosed with lung cancer | Moderate |
| Kocher et al., 2015 Longitudinal Analysis of 2293 NSCLC patients: a Comprehensive Study from the TYROL registry | Retrospective | Adult NSCLC patients = 2293 | No comparison<br><br>Presenting symptoms of lung cancer patients were determined | Most common symptoms of lung cancer patients at diagnosis: Coughing (54.7%), Dyspnea (62.1%)<br>-Cancer was diagnosed incidentally in 18.3%. 37.8% of them were stage I<br>Most of asymptomatic patients were diagnose at earlier stages than symptomatic patients.<br>Most common patient characteristics: Age over 50 (mean age 64.1), Male (70.3%) | Most common presenting symptoms in patients diagnosed with lung cancer are cough and dyspnea.<br>Age greater than 50 years and male gender are additional risk factors. | Low |

<table>
<tr>
<td>Irwin et al., 2006<br>Diagnosis and Management of Cough Executive Summary: ACCP evidence-based clinical practice guidelines</td>
<td>ACCP Evidence-Based Clinical Practice Guidelines<br><br>ACCP: American College of Chest Physicians</td>
<td>Adult patients</td>
<td>XR versus no imaging in patients complaining of cough</td>
<td>N/A</td>
<td>If cough is associated with risk factors for lung cancer, a chest x-ray should be obtained. Medical history is paramount in determining the need for x-ray imaging (e.g. smoker, evidence of systemic disease)</td>
<td>Low</td>
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<td>Hamilton et al., 2005<br>What are the clinical features of lung cancer before the diagnosis is made? A population-based case-control study</td>
<td>Retrospective Case Control Study<br><br>21 general practices data searched</td>
<td>N=1482<br><br>247 cases of primary lung cancer matched with 1235 controls by age sex and general practice (Age>=40 years)</td>
<td>No Comparison<br><br>Identifying prediagnostic features of lung cancer</td>
<td>86% of lung cancer patients were older than 60 years; 69% were male<br>Cough seen in 65% of cancer cases<br>Symptoms associated with cancer:
<table>
<tr><th>Symptom</th><th>Likelihood ratio</th></tr>
<tr><td>Hemoptysis</td><td>13</td></tr>
<tr><td>Weight loss</td><td>6.2</td></tr>
<tr><td>Appetite loss</td><td>4.8</td></tr>
<tr><td>Dyspnea</td><td>3.6</td></tr>
<tr><td>Chest or rib pain</td><td>3.3</td></tr>
<tr><td>Fatigue</td><td>2.3</td></tr>
<tr><td>Cough</td><td>2.2 first visit<br>3.2 second visit<br>4.2 third visit</td></tr>
<tr><td>Clubbing</td><td>55</td></tr>
</table>
PPV of these symptoms in smokers and ex-smokers were double those of non-smokers<br>20% of cancer cases had hemoptysis versus 1.5% of controls</td>
<td>Chest X-ray is recommended for unexplained cough persisting for 3 weeks or more</td>
<td>Moderate</td>
</tr>
<tr>
<td>Buccheri & Ferrigno, 2004<br>Lung cancer: clinical presentation and specialist referral time</td>
<td>Retrospective</td>
<td>N=1277 consecutive unselected patients with cytologically or histologically</td>
<td>Clinical manifestations of lung cancer</td>
<td>Incidental lung cancer in 12% of the sample<br>Alarming Symptoms:<br>Bloody sputum and cough =17%<br>Chest pain =15%<br>Dyspnea = 12%</td>
<td>Early characterization of symptom pattern improves early diagnosis rate of lung cancer and reduces time to referral</td>
<td>Low</td>
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| | | proven lung cancer | | Bloody sputum was more commonly reported with squamous cell lung cancers<br><br>Dyspnea, chest pain more frequent than expected in small cell lung carcinomas | | |
| Initial QOE Score Across Studies for PICO #1**: Low (3)** | | | | | | |

| SEMPI Grading QOE – Table 2A.1b – Risk of Bias | | |
|---|---|---|
| PICO #1: What clinical predictors warrant initial chest XR in adults with risk factors for lung cancer for optimal diagnostic assessment? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score Across Studies for PICO: **LOW** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of Bias | Serious | Selective reporting of data<br>No reporting of patients w/out lung cancer<br>No reporting of missed cases |
| Inconsistency | Not Serious | |
| Indirectness | Not Serious | |
| Imprecision | Not Serious | |
| **Positive Bias** | | |
| Strength of Association | Moderate | Likelihood Ratios presented for risk factors |
| Other Considerations | No | |
| **Overall Effect of Bias on Initial QOE Grade: No Change** | | |
| Final QOE Grade for Outcome Across Studies: **LOW** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

## SEMPI Grading QOE – Table 2A.1c – Evidence to Recommendations

**PICO #1:** What clinical predictors warrant initial chest XR in adults with risk factors for lung cancer for optimal diagnostic assessment?

### SEMPI Quality of Evidence (QOE) & Recommendation Strength

| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
|---|---|---|---|---|
| Okoli et al., 2018<br>Is symptom-based diagnosis of lung cancer possible? A systematic review and meta-analysis of symptomatic lung cancer prior to diagnosis for comparison with real-time data from routine general practice | To avoid false negative X-ray results in patients subsequently diagnosed with lung cancer, symptomatology and risk factors should be considered to improve diagnostic assessment | Moderate | Low (3) | Consensus (B) |
| Neal et al., 2017<br>Immediate chest X-ray for patients at risk of lung cancer presenting in primary care: randomised controlled feasibility trial | Chest x-ray findings are often normal in symptomatic patients, later diagnosed with lung cancer | Moderate | | |
| Kocher et al., 2015<br>Longitudinal Analysis of 2293 NSCLC patients: a Comprehensive Study from the TYROL registry | Most common presenting symptoms in patients diagnosed with lung cancer are cough and dyspnea. Age greater than 50 years and male gender are additional risk factors. | Low | | |
| Irwin, et al., 2006<br>Diagnosis and Management of Cough Executive Summary: ACCP evidence-based clinical practice guidelines | If cough is associated with risk factors for lung cancer, a chest x-ray should be obtained. Medical history is paramount in determining the need for x-ray imaging (e.g. smoker, evidence of systemic disease) | Low | | |
| Hamilton et al., 2005<br>What are the clinical features of lung cancer before the diagnosis is made? A population-based case-control study | Chest X-ray is recommended for unexplained cough persisting for 3 weeks or more | Moderate | | |
| Buccheri & Ferrigno, 2004<br>Lung cancer: clinical presentation and specialist referral time | Early characterization of symptom pattern improves early diagnosis rate of lung cancer and reduces time to referral | Low | | |

**Recommendation Rating: 3B**—Consensus recommendation for the intervention based on low quality evidence
**Justification:** Risk of bias insufficient to downgrade QOE given likelihood ratios provided. Consensus recommendation made as there is insufficient high-quality, trial-based evidence, and the primary support for recommendation lies in expert opinion and current clinical practice.

**Rating Definitions**:

**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**

**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus

**Conclusion:** Although there is insufficient high-quality evidence to guide the recommendation for chest x-ray (XR) evaluation of cough in patients with risk factors for lung cancer, the primary support lies in expert opinion and current clinical practice. Given the paucity of evidence-based data, it seems most prudent to use chest XR as the initial imaging modality to assess patients at increased risk for lung cancer (e.g. older age, persistent symptoms, smoking history, male gender) based upon a thorough history and physical exam.

**Final Recommendation**: **3B**—The following clinical predictors warrant initial chest x-ray (XR) imaging in patients with lung cancer risk factors (heavy smoker, age, male gender) to optimize diagnostic assessment:

- Cough duration 3 weeks or longer
- Dyspnea
- Hemoptysis

**PICO #2**: In adults with chest XR findings suggestive of malignancy, is computed tomography (CT) imaging of the chest warranted for further diagnostic assessment?

| SEMPI Grading QOE – Table 2A.2a – Summary of Findings | | | | | | |
|---|---|---|---|---|---|---|
| **PICO #2**: In adults with chest XR findings suggestive of malignancy, is computed tomography (CT) imaging of the chest warranted for further diagnostic assessment? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Beigelman-Aubry et al., 2016<br>CT imaging in pre-therapeutic assessment of lung cancer | Review | N/A | CT<br>(no comparator) | CT of chest/upper abdomen with contrast provides T-, M-, N-staging<br>Formal signs of vascular invasion (e.g. endovascular growth or perivascular cuffing) are identified by CT<br>Non-localized lesions on CT exam require histologic evaluation to determine surgical candidacy in lung cancer setting | Thin-section, volumetric enhanced CT of the chest, upper abdomen and supra-clavicular region is a reliable, pretherapeutic, assessment tool in patients with chest x-ray findings suggestive of malignancy | Low |
| Stamatis, 2015<br>Staging of lung cancer: the role of noninvasive, minimally invasive and invasive techniques | Review of professional society guidelines including: European Society of Thoracic Surgeons, American College of Chest Physicians, International Association for the Study of Lung Cancer, German Cancer Society | N/A | N/A | Computed tomography (CT) imaging of the chest is recommended for initial primary tumor evaluation due to high sensitivity (98-100%), restaging with CT after induction therapy is unclear<br><br>Diagnostic accuracy of CT is lacking for mediastinal lymph node involvement such that invasive biopsy procedures providing cyto-histology are required | Enhanced computed tomography (CT) imaging of the chest and upper abdomen, including the liver and adrenal glands, is recommended for initial primary tumor imaging in suspected lung cancer | Low |
| Silvestri et al., 2013<br>Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians | Systematic review update of 2006 American College of Chest Physicians (ACCP) guidelines | N/A | N/A | CT imaging of the chest provides anatomic detail identifying tumor location and proximity to local structures<br><br>The accuracy of chest CT imaging in differentiating benign from malignant mediastinal lymph nodes | Enhanced computed tomography (CT) imaging provides an initial presumptive definition of the clinical stage of known or suspected lung cancer | Moderate |

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| evidence-based clinical practice guidelines | | | | is unacceptably low (sensitivity/specificity=55%/81%) | | |
| Seemann et al., 2000 Differentiation of malignant from benign solitary pulmonary lesions using chest radiography, spiral CT and HRCT | Prospective, consecutive enrollment<br><br>CXR=chest XR<br>SCT=spiral CT<br>HRCT=high-resolution CT | N=104<br><br>MSPL-malignant solitary pulmonary lesions | CXR vs SCT vs HRCT | With a significance level of $p < 0.01$—Identification of MSPLs using **CXR**: sensitivity of 64.2% and specificity of 82.6% (diagnostic accuracy of 68.3%) Identification of MSPLs using **SCT**: sensitivity of 88.9% and specificity of 60.9% (diagnostic accuracy of 82.7%) Identification of MSPLs using **HRCT**: sensitivity of 91.4% and specificity of 56.5% (diagnostic accuracy of 83.7%) | Spiral CT and high-resolution CT of the chest are useful in differentiating malignant from benign pulmonary lesions as they provide a precise morphological assessment of the periphery of the pulmonary lesion and the adjacent visceral pleura | Moderate |
| Initial QOE Score Across Studies for PICO #2: **Moderate (2)** | | | | | | |

| SEMPI Grading QOE – Table 2A.2b – Risk of Bias | | |
|---|---|---|
| **PICO #2:** In adults with chest XR findings suggestive of malignancy, is computed tomography (CT) imaging of the chest warranted for further diagnostic assessment? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score Across Studies for PICO: **MODERATE** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of Bias | Not Serious | Review articles pose risk of bias; paucity of current trial-based data assessing role of imaging |
| Inconsistency | Not Serious | |
| Indirectness | Not Serious | |
| Imprecision | Not Serious | |
| **Positive Bias** | | |
| Strength of Association | Moderate | Consistency of uniform recommendations for CT as first step in imaging for suspected/known lung cancer |
| Other Considerations | No | Professional guidelines updated with systematic reviews |
| **Overall Effect of Bias on Initial QOE Grade: No change** | | |
| Final QOE Grade for Outcome Across Studies: **Moderate** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

## SEMPI Grading QOE – Table 2A.2c – Evidence to Recommendations

**PICO #2:** In adults with chest XR findings suggestive of malignancy, is computed tomography (CT) imaging of the chest warranted for further diagnostic assessment?

### SEMPI Quality of Evidence (QOE) & Recommendation Strength

| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
|---|---|---|---|---|
| Beigelman-Aubry et al., 2016<br>CT imaging in pre-therapeutic assessment of lung cancer | Thin-section, volumetric enhanced CT of the chest, upper abdomen and supraclavicular region is a reliable, pre-therapeutic, assessment tool in patients with chest x-ray findings suggestive of malignancy | Low | Moderate (2) | Strong (A) |
| Stamatis, 2015<br>Staging of lung cancer: the role of noninvasive, minimally invasive and invasive techniques | Contrast-enhanced computed tomography (CT) imaging of the chest and upper abdomen, including the liver and adrenal glands, is recommended for initial primary tumor imaging in suspected lung cancer | Low | | |
| Silvestri et al., 2013<br>Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines | Contrast-enhanced computed tomography (CT) imaging provides an initial presumptive definition of the clinical stage of known or suspected lung cancer | Moderate | | |
| Seemann et al., 2000<br>Differentiation of malignant from benign solitary pulmonary lesions using chest radiography, spiral CT and HRCT | Spiral CT and high-resolution CT of the chest are useful in differentiating malignant from benign pulmonary lesions as they provide a precise morphological assessment of the periphery of the pulmonary lesion and the adjacent visceral pleura | Moderate | | |

**Recommendation Rating: 2A**—Strong recommendation for the intervention based on moderate quality evidence
**Justification:** Risk of bias insufficient to downgrade QOE and consistency of findings in the literature and updated evidence-based professional society guidelines support a strong recommendation

**Rating Definitions**:

**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**
**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus

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| **Conclusion:** Multiple studies have demonstrated the value of computed tomography (CT) as the first advanced imaging study to evaluate suspected/known lung cancer. Recent review articles and professional society guidelines endorse the primacy of CT imaging with contrast in this situation. Anatomical detail of the primary tumor, its relation to and/or invasion of adjacent structures, airway integrity, assessment of regional lymph nodes and presence of metastases to liver and/or adrenal glands can be identified with contrast-enhanced CT imaging. Such information is essential in determining "next steps" in staging of pulmonary tumors. |
| **Final Recommendation**: **2A**— In adults with chest x-ray (XR) findings that suggest possible lung malignancy, chest computed tomography (CT) with contrast is recommended for initial evaluation and assessment. |

**PICO #3:** In adults with chest lesions requiring biopsy, what clinical parameters favor endobronchial ultrasound guided (EBUS) vs CT-guided transthoracic needle biopsy for optimal diagnostic accuracy?

| SEMPI Grading QOE – Table 2A.3a – Summary of Findings | | | | | | |
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| **PICO #3:** In adults with chest lesions requiring biopsy, what clinical parameters favor endobronchial ultrasound guided (EBUS) vs CT-guided transthoracic needle biopsy for optimal diagnostic accuracy? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Han et al., 2018 Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: A systematic review and meta-analysis | Systematic review and meta-analysis | N=24 9 articles on the bronchoscopic (BR) approach and 15 articles on the percutaneous (PC) approach | Transbronchial lung biopsy using radial endobronchial ultrasound and virtual bronchoscopic navigation (TBLB-rEBUS&VBN) and CT-guided transthoracic needle biopsy (CT-TNB) | Pooled diagnostic yield (CI): BR: 75% (69–80) approach and PC: 93% (90–96) For PLs ≤ 2 cm, the PC approach (pooled diagnostic yield: 92%, (95% CI: 88–95) superior to the BR approach 66%, (95% CI: 55–76).<br><br>Complications of pneumothorax and hemorrhage rare with the bronchoscopic approach but common with the percutaneous approach. For lesions greater than 2 cm, the BR approach may be considered for its diagnostic yield of over 80% | CT- guided transthoracic needle biopsy has higher diagnostic yield than radial endobronchial ultrasound and virtual bronchoscopic navigation for the evaluation of peripheral lesions. | Moderate |
| Zhu et al., 2018 A prospective study on the diagnosis of peripheral lung cancer using endobronchial ultrasonography with a guide sheath and computed tomography-guided transthoracic needle aspiration | Prospective study | N=158 – EBUS-GS N=177-CT-TTNA (with peripheral pulmonary lesions on CT) distance of lesions to the chest wall was >80 mm in the EBUS-GS group and ⩽80 mm in the CT-TTNA group | Endobronchial ultrasonography with a guide sheath (EBUS-GS) vs computed tomography-guided transthoracic needle aspiration CT-TTNA | Diagnostic rates: EBUS-GS- 64% CT-TTNA-97.7% (p= 0.001) Incidence of complications in the EBUS-GS group was significantly less than that in the CT-TTNA group (p=0.001) EBUS-GS group, the size of PPLs in 62.7% patients were <30 mm | For peripheral lung lesions endobronchial ultrasonography with a guided sheath has lower diagnostic rate compared to computed tomography-guided transthoracic needle aspiration | Moderate |

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| Bonifazi et al., 2017 Conventional versus Ultrasound-Guided Transbronchial Needle Aspiration for the Diagnosis of Hilar/Mediastinal Lymph Adenopathies: A Randomized Controlled Trial | Prospective, randomized study | N= 253 (randomized to either EBUS-TBNA (n = 127) or c-TBNA (n = 126)) | Conventional transbronchial needle aspiration (c-TBNA) vs endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) | Sensitivity of EBUS-TBNA higher, but not significant.<br>EBUS-TBNA 92% (95% CI:87-97) and c-TBNA: 82% (95% CI: 75-90), p > 0.05).<br><br>Sensitivity of staged strategy :94% | Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is preferred over c-TBNA for hilar/mediastinal lesions | High |
| Munir et al., 2017 Diagnostic Yield for Cancer and Diagnostic Accuracy of Computed Tomography–guided Core Needle Biopsy of Subsolid Pulmonary Lesions | Retrospective | 52 adult patients | Evaluation of CT guided needle biopsy (CTNB) of subsolid pulmonary lesions | Overall diagnostic yield and accuracy of CTNB were 80.8% and 84.6%, respectively<br><br>Diagnostic yield and accuracy were different between variable lesions:<br>• 57.1% and 51.7%, for pure ground glass (GG) lesions.<br>• 78.3% and 87% for GG-predominant.<br>• 90.9% and 90.9% for solid predominant lesions<br><br>The lesion size is not a statistically significant variable in diagnostic yield of cancer (P = 0.53)<br><br>17 patients had surgical biopsy. CTNB correlated with the surgical biopsy in 14 (82.5%) patients. | CT-guided core needle biopsy offers a high yield in establishing a histopathologic diagnosis of subsolid pulmonary lesions, with both GG and solid-predominance. It offers a relatively safe and accurate diagnostic technique that will affect patient management | Moderate |
| Navani et al., 2015 Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial | Prospective, randomized | N= 67 Conventional Diagnosis and Staging (44 bronchoscopy, 14 CT guided, 5 conventional TBNA, 1 mediastinoscopy, 2 PET-CT scan)<br>N=66 (EBUS-TBNA) | EBUS-TBNA vs conventional imaging | Median time-to-treatment decision longer after CDS (29 days [95% CI: 23–35]), than after EBUS (14 days [(95% CI:14–15]; HR 1·98, 95% CI: 1·39–2·82, p<0·0001)<br>EBUS-TBNA:<br>Sensitivity:92% (95% CI: 78–98)<br>Negative predictive value 90% (95% CI: 72–97)<br>Diagnostic accuracy was 95% (95% CI: 86–99) | Endobronchial ultrasound guided transbronchial needle aspiration should be considered as the initial investigation for patients with suspected lung cancer | Moderate |

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| Kim et al., 2008<br>Diagnostic Accuracy of CT-Guided Core Biopsy of Ground-Glass Opacity Pulmonary Lesions | Retrospective | Total patient = 50<br>Age range (43-78 years) | CT-guided core biopsy<br>Diagnostic accuracy<br>Compared <2 cm vs >= 2cm<br>And<br>GGO component >90%<br>Vs 50-90%<br><br>True positive cases were surgically confirmed | Malignancy diagnosis = 33 patients<br>False positive = 3 patients reconfirmed with repeated biopsy<br>Benign lesion diagnosis = 10 patients<br>Sensitivity =92%<br>Specificity =90%<br>Accuracy 91% | CT-guided core biopsy has high diagnostic accuracy for pulmonary lesions<br>It is a safe diagnostic alternative to surgical biopsy | Low |
| Yasufuku et al., 2006<br>Comparison of Endobronchial Ultrasound, Positron Emission Tomography, and CT for Lymph node Staging of Lung Cancer | Prospective | Total patients = 102<br>confirmed lung cancer =96<br><br>Radiologically suspected lung cancer =6<br>(Mean age =67.8 years) | CT, PET, EBUS-TBNA<br><br>Surgical histology was used as "gold standard" to confirm metastasis<br>Patients enrolled if they were eligible for curative thoracic surgery<br><br>All patients received above mentioned interventions<br><br>EBUS-TBNA performed after CT and PET scan | Number of lymph nodes biopsied:<br>Mediastinal=147<br>Hilar =53<br>Sensitivity:<br>CT-76.9%<br>PET-80.0%<br>EBUS-TBNA-92.3%<br>Specificity:<br>CT-55.3%<br>PET-70.1%<br>EBUS-TBNA-100%<br>Accuracy;<br>CT-60.8%<br>PET-72.5%<br>EBUS-TBNA-98.0% | EBUS-TBNA should be used early to evaluate mediastinal nodes in staging process of lung cancer | Moderate |

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|---|---|---|---|---|---|---|
| Herth et al., 2006<br>Real-time endobronchial ultrasound guided trans bronchial needle aspiration for sampling mediastinal lymph nodes | Prospective (Consecutive enrollment) | Total patients = 502<br>Mean age =59 years | EBUS-TBNA<br><br>Patients referred for TBNA of mediastinal lymph nodes | Biopsied nodes =572<br>Diagnosis positive nodes= 535<br>Sensitivity -94%<br>Specificity-100%<br>Accuracy-94%<br>No complications reported.<br>Mean diameter of nodes punctured - 1.6cm<br>Range 0.8cm-3.2 cm | EBUS-TBNA is a safe, highly sensitive and specific method to stage mediastinal lymph nodes | Moderate |
| Ohno et al., 2003<br>CT-Guided Transthoracic Needle Aspiration Biopsy of Small (<=20mm) Solitary Pulmonary Nodules | Prospective | Total patients =162<br>Mean age =67 years | CT-guided transthoracic needle aspiration biopsy | Overall diagnostic accuracy =77.2%<br>103/162 diagnosed as malignant nodules<br>22 were benign cases<br>37 [(15 benign and 22 malignant) (false positive and false negative)]<br><br>Lesion size and accuracy<br>=<10mm: 52% accuracy<br>11-15mm:74.4% accuracy<br>16-20mm-91.5% accuracy<br>Pneumothorax rate=28.4% (comparable to other biopsy modalities) | The diagnostic accuracy of CT-guided aspiration biopsy is directly proportional to lesion size<br><br>Accuracy is highest for lesions ≥ 10mm in size | Moderate |
| Charig & Phillips, 2000<br>CT-Guided Cutting Needle Biopsy of Lung Lesions --Safety and Efficacy of an Out-patient Service | Prospective (Consecutive enrollment) Outpatient setting | Total patients =183<br>Number of biopsies =185 | CT-guided cutting needle biopsy | Malignant histology=150 biopsies<br>Benign =23 biopsies<br>False negative =12<br>No false positive<br>Sensitivity =92.6%<br>Specificity=100%<br>Accuracy =93.5%<br>Pneumothorax occurred in 48 patients (25.9%) | CT-guided biopsy of pulmonary lesions is a safe technique with high diagnostic accuracy and complication rates similar to other biopsy approaches. It can be safely performed as an outpatient procedure | Moderate |
| Initial QOE Score Across Studies for PICO #3**: Moderate (2)** | | | | | | |

| SEMPI Grading QOE – Table 2A.3b – Risk of Bias | | |
|---|---|---|
| **PICO #3:** In adults with chest lesions requiring biopsy, what clinical parameters favor endobronchial ultrasound guided (EBUS) vs CT-guided transthoracic needle biopsy for optimal diagnostic accuracy? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score Across Studies for PICO: **MODERATE** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of Bias | Serious | Metanalysis with heterogenous literature and no bi-arm analysis<br>Consecutive enrollment of patients in some studies<br>In non-randomized studies attrition rates high leading to potential missed cases |
| Inconsistency | Serious | Heterogenous literature (different bronchoscopic techniques used) |
| Indirectness | Not Serious | |
| Imprecision | Not Serious | |
| **Positive Bias** | | |
| Strength of Association | Moderate | Findings are consistent between studies (CT- guidance for peripheral lesions and US-guided bronchoscopy for central lesions) |
| Other Considerations | Yes | Follow up procedures and reporting well documented for adverse events resulting from procedure |
| **Overall Effect of Bias on Initial QOE Grade: No Change** | | |
| Final QOE Grade for Outcome Across Studies: **MODERATE** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

| SEMPI Grading QOE – Table 2A.3c – Evidence to Recommendations | | | | |
|---|---|---|---|---|
| **PICO #3:** In adults with chest lesions requiring biopsy, what clinical parameters favor endobronchial ultrasound guided (EBUS) vs CT-guided transthoracic needle biopsy for optimal diagnostic accuracy? | | | | |
| SEMPI Quality of Evidence (QOE) & Recommendation Strength | | | | |
| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
| Han et al., 2018<br>Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: A systematic review and meta-analysis | CT- guided transthoracic needle biopsy has higher diagnostic yield than radial endobronchial ultrasound and virtual bronchoscopic navigation for the evaluation of peripheral lesions. | Moderate | Moderate (2) | Strong (A) |
| Zhu et al., 2018<br>A prospective study on the diagnosis of peripheral lung cancer using endobronchial ultrasonography with a guide sheath and computed tomography-guided transthoracic needle aspiration | For peripheral lung lesions endobronchial ultrasonography with a guided sheath has lower diagnostic rate compared to computed tomography-guided transthoracic needle aspiration | Moderate | | |
| Bonifazi et al., 2017<br>Conventional versus Ultrasound-Guided Transbronchial Needle Aspiration for the Diagnosis of Hilar/Mediastinal Lymph Adenopathies: A Randomized Controlled Trial | Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is preferred over c-TBNA for hilar/mediastinal lesions. | High | | |
| Munir et al., 2017<br>Diagnostic Yield for Cancer and Diagnostic Accuracy of Computed Tomography–guided Core Needle Biopsy of Subsolid Pulmonary Lesions | CT-guided core needle biopsy offers a high yield in establishing a histopathologic diagnosis of subsolid pulmonary lesions, with both GG and solid-predominance. It offers a relatively safe and accurate diagnostic technique that will affect patient management | Moderate | | |

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| Navani et al., 2015<br>Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial | Endobronchial ultrasound guided transbronchial needle aspiration should be considered as the initial investigation for patients with suspected lung cancer | Moderate | | |
| Kim et al., 2008<br>Diagnostic Accuracy of CT-Guided Core Biopsy of Ground-Glass Opacity Pulmonary Lesions | CT-guided core biopsy has high diagnostic accuracy for pulmonary lesions It is a safe diagnostic alternative to surgical biopsy | Low | | |
| Yasufuku et al., 2006<br>Comparison of Endobronchial Ultrasound, Positron Emission Tomography, and CT for Lymph node Staging of Lung Cancer | EBUS-TBNA should be used early to evaluate mediastinal nodes in staging process of lung cancer | Moderate | | |
| Herth et al., 2006<br>Real-time endobronchial ultrasound guided trans bronchial needle aspiration for sampling mediastinal lymph nodes | EBUS-TBNA is a safe, highly sensitive and specific method to stage mediastinal lymph nodes | Moderate | | |
| Ohno et al., 2003<br>CT-Guided Transthoracic Needle Aspiration Biopsy of Small (<=20mm) Solitary Pulmonary Nodules | The diagnostic accuracy of CT-guided aspiration biopsy is directly proportional to lesion size<br>Accuracy is highest for lesions > 10 mm in size | Moderate | | |
| Charig & Phillips, 2000<br>CT-Guided Cutting Needle Biopsy of Lung Lesions --Safety and Efficacy of an Out-patient Service | CT-guided biopsy of pulmonary lesions is a safe technique with high diagnostic accuracy and complication rates similar to other biopsy approaches. It can be safely performed as an outpatient procedure | Moderate | | |

**Recommendation Rating: 2A—** Strong recommendation for the intervention based on moderate quality evidence
**Justification:** Risk of bias insufficient to downgrade despite heterogeneity due to randomization and consistent accuracy estimates with evidence supporting CT guidance for peripheral lesions and US-guided bronchoscopic techniques for central lesions.

**Rating Definitions**:

**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**
**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus

**Conclusion:** Patients with suspected lung cancer require a tissue-based diagnosis. Histopathologic diagnosis of lung cancer can be obtained by the least invasive and the safest method, depending on the patient's characteristics (localization of the lesion, respiratory function) and on the availability of diagnostic means. The aims of tissue sampling include confirmation of diagnosis and molecular testing. The two main methods to obtain adequate biopsy samples are endobronchial ultrasound-guided (EBUS) and computed tomography (CT)-guided lung biopsy.

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| Bronchoscopic biopsies are helpful for central tumors, whereas CT-guided biopsies are more suitable for peripheral lesions. In case of mediastinal involvement (mediastinal direct tumoral invasion or enlarged mediastinal lymph nodes), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can be performed for both primary diagnosis and staging. High feasibility of performing molecular analysis on specimens obtained by EBUS-TBNA has been reported. On the other hand, CT-guided lung biopsy is more accurate for peripheral tumors offering a 90% sensitivity for the diagnosis of lung cancer (Zhang et al., 2016). The main disadvantage of the CT-guided lung biopsy is the higher incidence of complications, such as pneumothorax and pulmonary hemorrhage (Tomiyama et al., 2006; Wiener et al., 2013). |
| **Final Recommendation: 2A**—In adult patients with chest lesions requiring biopsy, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is recommended for central lesions (mediastinal, hilar). For larger peripheral lesions (e.g. chest wall), CT-guided transthoracic needle aspiration (CT- TTNA) is recommended. |

**PICO #4:** In adults with cancer of the lung, should PET-CT imaging be performed to stage the tumor compared to other imaging for optimal patient management?

| SEMPI Grading QOE – Table 2A.4a – Summary of Findings | | | | | | |
|---|---|---|---|---|---|---|
| **PICO #4:** In adults with cancer of the lung, should PET-CT imaging be performed to stage the tumor compared to other imaging for optimal patient management? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Taylor et al., 2019 Diagnostic accuracy of whole-body MRI versus standard imaging pathways for metastatic disease in newly diagnosed non-small-cell lung cancer: the prospective Streamline L trial | Prospective, multicenter pragmatic clinical trial (real world settings) | 976 patients (across 16 hospital)<br><br>Only 353 participated in the study | 18F-FDG PET-CT<br><br>versus<br><br>Whole-body magnetic resonance imaging (WB-MRI) | No statistical difference in staging **specificity** between WB-MRI (93% [95% CI: 88–96]) and PET-CT (95% [95% CI: 91–98], p=0.45) and **sensitivity** between WB-MRI (50% [95% CI: 37–63) and PET-CT (54% [95% CI: 41–67], p=0.73)<br><br>Both modalities offered agreement for N & T staging as well as agreement for treatment decisions. Median time to staging is shorter for WB-MRI (13 days [12–14] vs PET-CT (19 days [17–21]). Mean per-patient costs were also lower for WB-MRI compared to PET-CT (£317 [273–361]) vs (£620 [574–666] | Whole body-magnetic resonance imaging (WB-MRI) and PET-CT have similar diagnostic accuracy for identifying patients with metastatic disease in newly diagnosed non-small cell lung cancer (NSCLC), and lead to similar treatment decisions. WB-MRI offers greater cost and time savings | Low |

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|---|---|---|---|---|---|---|
| Kirchner et al., 2019 Prospective comparison of 18 F-FDG PET/MRI and 18 F-FDG PET/CT for thoracic staging of non-small cell lung cancer | Prospective study (unblinded and randomized) | 84 patients | 18F-FDG PET/MRI Vs 18F-FDG PET/CT | 97.4% concordance rate for T-stage categorization with 18F-FDG PET/CT correctly determining the T-stage in 92.3% of patients while 18F-FDG PET/MRI in 89.7%.<br><br>98.8% concordance rate in N-stage categorization with 18F-FDG PET/CT correctly determining the T-stage in 92.9% of patients while 18F-FDG PET/MRI in 91.7%.<br><br>T and N staging accuracy were not statistically significant in both protocols ($p > 0.5$, each) while tumor size and SUVmax measurements derived from both imaging modalities had excellent correlation ($r = 0.963$ and $r = 0.901$, respectively) | 18F-FDG PET/MRI and 18F-FDG PET/CT both show a high diagnostic performance for T and N staging in patients suffering from NSCLC but 18F-FDG PET/CT shows and validates its superiority over 18F-FDG PET/MRI (though not statistically significant) | Moderate |
| Kishida et al., 2018 Performance Comparison Between 18F-FDG PET/CT Plus Brain MRI and Conventional Staging Plus Brain MRI in Staging of Small Cell Lung Carcinoma | Prospective study | 59<br><br>CECT = Contrast enhance CT WB = whole body | FDG PET/CT - brain MR versus conventional staging (histopathologic confirmation)<br><br>Conventional staging = WB CECT, contrast-enhanced brain MR, and bone scintigraphy | Diagnostic accuracy of PET/CT for N factor and TNM stage (N, 89.8% [53/59]; TNM stage, 88.1% [52/59]) was significantly higher than that of conventional staging plus enhanced brain MR (N, 67.8% [40/59], $p = 0.0002$; TNM stage, 72.9% [43/59], $p = 0.004$). | FDG PET/CT with contrast-enhanced brain MR is potentially equal to or more effective than conventional staging plus enhanced brain MR for T, N, and M assessment and TNM and VALSG staging of SCLC | Moderate |

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|---|---|---|---|---|---|---|
| Yu et al., 2018<br>Clinical usefulness of 18-FDG PET/CT for the detection of distant metastases in patients with non-small cell lung cancer at initial staging: a meta-analysis | Meta-analysis | 10 studies<br>(1333 patients) | No comparator. Reviewing the diagnostic parameters of FDG PET/CT for distant metastasis detection in the initial staging of NSCLC | Sensitivity = 0.81<br>Specificity = 0.96<br>Diagnostic odds ratio (DOR) = 117<br>Negative Likelihood ratio (NLRs) = 0.20<br>Positive likelihood ratios (PLRs) = 22.9<br>(PET/CT has 23 times higher probability of detecting distant metastasis in patients with NSCLC) | FDG PET/CT has an excellent diagnostic accuracy for the detection of distant metastasis in the initial staging of NSCLC and may also possess the ability to detect the metastasis to distant areas earlier. | Moderate |
| Schmidt-Hansen et al., 2014<br>PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer | Meta-analysis | 6095 Adults across<br>45 Studies | (+) PET-CT versus surgical pathology findings (gold standard) | Overall PET-CT Sensitivity 77.4% (95% CI: 65.3-86.1) Specificity 90.1% (95% CI: 85.3-93.5) when using activity > background as criterion for test positivity<br><br>When using SUV max ≥ 2.5 as a cutoff for positivity, PET-CT was 81.3% sensitive (95% CI: 70.2 – 88.9) and 79.4% specific (95% CI: 70 – 86.5)<br><br>Sensitivity and specificity were notably different between studies. This variability might be explained by difference country of origin, scanning equipment, predominant cancer subtype, FDG dose, and study size | PET-CT is central to the assessment of patients who might potentially be suitable for treatment with curative intent and is usually done after CT scan imaging. This test is able to define more clearly whether lung cancer has spread to lymph nodes or further.<br><br>Accuracy of PET-CT is insufficient to allow management based on PET-CT alone<br><br>Therefore, PET-CT should be used to direct clinicians to the next step: either to biopsy or surgery | Moderate |
| Initial QOE Score Across Studies for PICO #4: **Moderate (2)** | | | | | | |

| SEMPI Grading QOE – Table 2A.4b – Risk of Bias | | |
|---|---|---|
| **PICO #4:** In adults with confirmed cancer of the lung, should PET-CT imaging be performed to stage the tumor compared to other imaging for optimal patient management? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score across studies for PICO: **MODERATE** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of bias | Not Serious | Selective reporting of data with higher withdrawal and exclusion rates<br>Selection bias present |
| Inconsistency | Not Serious | |
| Indirectness | Not Serious | |
| Imprecision | Serious | Small sample size in 2 studies |
| **Positive Bias** | | |
| Strength of association | Moderate | Similar findings among studies<br>Confidence intervals acceptable |
| Other Considerations | No | |
| **Overall Effect of Bias on Initial QOE Grade: No Change** | | |
| Final QOE Grade for Outcome Across Studies: **MODERATE** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

## SEMPI Grading QOE – Table 2A.4c – Evidence to Recommendations

**PICO #4:** In adults with confirmed cancer of the lung, should PET-CT imaging be performed to stage the tumor compared to other imaging for optimal patient management?

### SEMPI Quality of Evidence (QOE) & Recommendation Strength

| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
|---|---|---|---|---|
| Taylor et al., 2019<br>Diagnostic accuracy of whole-body MRI versus standard imaging pathways for metastatic disease in newly diagnosed non-small-cell lung cancer: the prospective Streamline L trial | Whole body-magnetic resonance imaging (WB-MRI) and PET-CT have similar diagnostic accuracy for identifying patients with metastatic disease in newly diagnosed non-small cell lung cancer (NSCLC), and lead to similar treatment decisions.<br>WB-MRI offers greater cost and time savings | Low | Moderate (2) | Strong (A) |
| Kirchner et al., 2019<br>Prospective comparison of 18 F-FDG PET/MRI and 18 F-FDG PET/CT for thoracic staging of non-small cell lung cancer | 18F-FDG PET-MRI and 18F-FDG PET-CT both show a high diagnostic performance for T and N staging in patients suffering from NSCLC but 18F-FDG PET/CT shows and validates its superiority over 18F-FDG PET/MRI (though not statistically significant) | Moderate | | |
| Kishida et al., 2018<br>Performance Comparison Between 18F-FDG PET/CT Plus Brain MRI and Conventional Staging Plus Brain MRI in Staging of Small Cell Lung Carcinoma | FDG PET-CT with contrast-enhanced brain MR is potentially equal to or more effective than conventional staging plus enhanced brain MR for T, N, and M assessment and TNM and VALSG staging of SCLC | Moderate | | |
| Yu et al., 2018<br>Clinical usefulness of 18-FDG PET/CT for the detection of distant metastases in patients with non-small cell lung cancer at initial staging: a meta-analysis | FDG PET-CT has an excellent diagnostic accuracy for the detection of distant metastasis in the initial staging of NSCLC and may also possess the ability to detect the metastasis to distant areas earlier. | Moderate | | |
| Schmidt-Hansen et al., 2014<br>PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer | Accuracy of PET-CT is insufficient to allow management based on PET-CT alone; PET-CT should be used to direct clinicians to the next step: either to biopsy or surgery | Moderate | | |

**Recommendation Rating: 2A**—Strong recommendation for the intervention based on moderate quality evidence
**Justification:** Risk of bias insufficient to downgrade QOE

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| **Rating Definitions**:<br>**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**<br>**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus |
| **Conclusion:** In adults with confirmed lung cancer (either non-small cell lung cancer-NSCLC or small-cell lung cancer-SCLC), PET-CT imaging of the skull base to mid-thigh can be used for staging purposes and is comparable to conventional staging techniques (CT imaging alone). In adults with SCLC and stage III or higher NSCLC, magnetic resonance (MR) of the brain with and without contrast is included in staging protocols to identify metastatic spread to the brain. Although there is emerging data regarding the comparability of whole body-magnetic resonance imaging (WB-MRI) to PET-CT in the staging of lung cancer, there is inadequate data and lack of consensus at present to make this recommendation. |
| **Final Recommendation**: **2A**— In adult patients with **small cell lung cancer** (**SCLC**), PET-CT (skull base to mid-thigh) imaging plus magnetic resonance (MR) of the brain without and with contrast is recommended to stage the disease. When PET-CT is unavailable, CT without and with contrast of the head, chest, abdomen/pelvis is recommended.<br>In adult patients with **non-small cell lung cancer (NSCLC**), PET-CT (skull base to mid-thigh) imaging is recommended for initial staging. When PET-CT is unavailable, CT without and with contrast of the head, chest, abdomen/pelvis is recommended. |

**PICO #5**: In adults with lung cancer where bone metastases are suspected, which imaging modality is preferred for optimal diagnostic accuracy?

| SEMPI Grading QOE – Table 2A.5a – Summary of Findings | | | | | | |
|---|---|---|---|---|---|---|
| **PICO #5:** In adults with lung cancer where bone metastases are suspected, which imaging modality is preferred for optimal diagnostic accuracy? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Zhang et al., 2015 A comparative study of 18 F-fluorodeoxyglucose positron emission tomography/computed tomography and 99m Tc-MDP whole-body bone scanning for imaging osteolytic bone metastases | Retrospective comparative Study | 34 patients (21 with lung cancer) | F-FDG PET-CT versus Tc-MDP whole body bone scan<br><br>Reference standard—histopathologic confirmation | 21 patients with primary lung cancer<br><br>Sensitivity:<br>18F-FDG PET-CT: 92.9%<br>Tc-MDP: 58.3%<br>($p < 0.001$) | 18F-FDG PET-CT has higher sensitivity to detect metastatic bone lesions compared to Tc-MDP whole body bone scintigraphy in patients with primary lung cancer | Low |
| Silvestri et al., 2013 Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines | American College of Chest Physicians Clinical Practice Guidelines | Adults | Comparison of imaging modalities to surgical pathology specimens (reference standard) | N/A | Bone scintigraphy can be used when PET or PET-CT is not available or is inconclusive.<br>Of note, bone scintigraphy has a high false positive rate due to the high prevalence of degenerative and traumatic skeletal disease in the general population | Moderate |
| Qu et al., 2012 A meta-analysis of 18FDG-PET-CT, 18FDG-PET, MRI, and bone scintigraphy for diagnosis of bone | Meta-analysis | 2940 adult patients<br>(17 studies) | PET-CT vs PET vs MR vs Bone Scan (BS) to detect bone metastasis | Sensitivities (pooled) for detection of bone metastasis:<br>PET-CT = 92% (95% CI: 0.88-0.95)<br>PET = 87% (95% CI: 0.81-0.92)<br>MR = 77% (95% CI: 0.65-0.87)<br>BS = 86% ((5% CI: 0.82-0.89) | PET-CT has higher sensitivity and specificity for metastatic bone lesions in lung cancer patients; magnetic resonance (MR) imaging can be | Moderate |

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| metastases in patients with lung cancer | | | | Specificities (pooled) for the detection of bone metastasis:<br>PET-CT = 98% (95% CI: 0.97-0.98)<br>PET = 94% (95% CI: 0.92-0.96)<br>MR = 92% (95% CI: 0.88-0.95)<br>BS = 88% (95% CI: 0.86-0.89)<br>Pooled DORs (diagnostic odds ratio):<br>PET-CT = 449.17 (p<0.001)<br>PET = 118.25 (p<0.001)<br>MR = 38.27 (p<0.001)<br>BS = 63.37 (p<0.001) | used when suspected lesions cross tissue planes involving multiple structures | |
| Liu et al., 2011<br><br>Fluorine-18 deoxyglucose positron emission tomography, magnetic resonance imaging and bone scintigraphy for the diagnosis of bone metastases in patients with lung cancer: which one is the best? --a meta-analysis. | Meta-analysis | 5676 Adults (17-89 years) | PET-CT vs PET vs MRI vs bone scintigraphy (BS) for diagnosing bone metastases | Pooled sensitivities in detecting bone metastases:<br>PET: 92% (95% CI: 89 – 94)<br>PET-CT: 95% (95% CI: 91 – 97)<br>MRI: 80% (95% CI: 69 – 89)<br>BS: 92% (95% CI: 89 – 94)<br>PET-CT was more sensitive than PET (P < 0.05).<br>Pooled specificities in detecting bone metastases:<br>PET: 97% (95% CI: 96- 98)<br>PET-CT: 98% (95% CI: 97 – 98)<br>MRI: 91% (95% CI: 89 – 94)<br>BS: 69% (95% CI: 66 -- 72)<br>The specificity of PET and PET-CT were not statistically different. | PET-CT is the most sensitive imaging modality for detection of bone metastases in lung cancer patients | Moderate |
| Yang et al., 2011<br>Diagnosis of bone metastases: a meta-analysis comparing 18FDG PET, CT, MRI and bone scintigraphy | Meta-analysis | 15,221 adult patients (145 studies) | PET vs CT vs MR vs Bone Scan (BS) to detect bone metastasis | Sensitivities (pooled) for detection of bone metastasis:<br>MR = 90.6%<br>PET = 89.7%<br>BS = 86.0%<br>CT = 72.9%<br>Conclusion: **PET=MR > BS > CT**<br>Specificities (pooled) for detection of bone metastasis:<br>PET = 96.8%<br>MR = 95.4%<br>CT = 94.8%<br>BS = 84.1%<br>Conclusion: **PET=MR=CT > BS** | PET and MR imaging are comparable in diagnostic accuracy and significantly more accurate than CT or Bone Scintigraphy for identifying bone metastases in lung cancer patients | Moderate |

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|---|---|---|---|---|---|---|
| Song et al., 2009 Efficacy comparison between (18)F-FDG PET/CT and bone scintigraphy in detecting bony metastases of non-small cell cancer | Retrospective Review | 1000 adult NSCLC patients who staging involved both PET/CT and bone scan<br><br>105 (10.5%) with confirmed bone metastasis form the study group | PET/CT vs Bone Scan (BS) to detect bone metastasis | -Detection of bone metastasis:<br>**PET/CT**:<br>Sensitivity = 94.3%<br>Specificity = 98.8%<br>(p=0.001)<br>**Bone scan**:<br>Sensitivity = 78.1%<br>Specificity = 97.4%<br>(p=0.006)<br>PET/CT also demonstrated lower incidence of false positive (1.2% vs 2.9%) and false-negative results (5.7% vs 21.9%) than bone scan<br><br>PET-CT was statistically more sensitive and specific than bone scan (P-values = 0.001 and 0.006 respectively) in detecting bone metastases. | PET-CT is superior to bone scintigraphy in detecting bone metastasis in patients with non-small cell lung cancer | Low |
| Initial QOE Score Across Studies for PICO #5: **Moderate (2)** | | | | | | |

| SEMPI Grading QOE – Table 2A.5b – Risk of Bias | | |
|---|---|---|
| **PICO #5:** In adults with lung cancer where bone metastases are suspected, which imaging modality is preferred for optimal diagnostic accuracy? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score Across Studies for PICO: **MODERATE** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of Bias | Serious | Retrospective data and Small N |
| Inconsistency | Not Serious | |
| Indirectness | Not Serious | |
| Imprecision | Not Serious | |
| **Positive Bias** | | |
| Strength of Association | Moderate | Strong statistical correlation, acceptable confidence intervals, Consensus exists among field experts |
| Other Considerations | No | |
| **Overall Effect of Bias on Initial QOE Grade: No Change** | | |
| Final QOE Grade for Outcome Across Studies: **MODERATE** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

| SEMPI Grading QOE – Table 2A.5c – Evidence to Recommendations | | | | |
|---|---|---|---|---|
| **PICO #5:** In adults with lung cancer where bone metastases are suspected, which imaging modality is preferred for optimal diagnostic accuracy? | | | | |
| SEMPI Quality of Evidence (QOE) & Recommendation Strength | | | | |
| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
| Zhang et al., 2015<br>A comparative study of 18 F-fluorodeoxyglucose positron emission tomography/computed tomography and 99m Tc-MDP whole-body bone scanning for imaging osteolytic bone metastases | 18F-FDG PET-CT has higher sensitivity to detect metastatic bone lesions compared to Tc-MDP whole body bone scintigraphy in patients with primary lung cancer | Low | Moderate (2) | Strong (A) |
| Silvestri et al., 2013<br>Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines | Bone scintigraphy can be used when PET or PET-CT is not available or is inconclusive. Of note, bone scintigraphy has a high false positive rate due to the high prevalence of degenerative and traumatic skeletal disease in the general population | Moderate | | |
| Qu et al., 2012<br>A meta-analysis of 18FDG-PET-CT, 18FDG-PET, MRI, and bone scintigraphy for diagnosis of bone metastases in patients with lung cancer | PET-CT has higher sensitivity and specificity for metastatic bone lesions in lung cancer patients; magnetic resonance (MR) imaging can be used when suspected lesions cross tissue planes involving multiple structures | Moderate | | |
| Liu et al., 2011<br>Fluorine-18 deoxyglucose positron emission tomography, magnetic resonance imaging and bone scintigraphy for the diagnosis of bone metastases in patients with lung cancer: which one is the best? --a meta-analysis. | PET-CT is the most sensitive imaging modality for detection of bone metastases in lung cancer patients | Moderate | | |
| Yang et al., 2011<br>Diagnosis of bone metastases: a meta-analysis comparing 18FDG PET, CT, MRI and bone scintigraphy | PET and MR imaging are comparable in diagnostic accuracy and significantly more accurate than CT or Bone Scintigraphy for identifying bone metastases in lung cancer patients | Moderate | | |
| Song et al., 2009<br>Efficacy comparison between (18)F-FDG PET/CT and bone scintigraphy in detecting bony metastases of non-small cell cancer | PET-CT is superior to bone scintigraphy in detecting bone metastasis in patients with non-small cell lung cancer | Low | | |

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| **Recommendation Rating: 2A**—Strong recommendation for the intervention based on moderate quality evidence<br>**Justification:** Meta-analyses with consistent conclusions support PET-CT as being more accurate than bone scintigraphy in the evaluation of lung cancer patients with suspected bone metastases; insufficient risk of bias to downgrade QOE |
| **Rating Definitions**:<br>**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**<br>**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus |
| **Conclusion:** The literature supports the use of PET-CT scan as the imaging modality of choice in adults with lung cancer, who are being evaluated for metastasis to bone. Data supporting this recommendation are derived primarily from non-small cell lung cancer (NSSLC) patients as clinical trial data in small-cell lung cancer (SCLC) patients are lacking. This approach has been adopted and accepted by clinical practice guideline committees. PET-CT is becoming increasingly popular as it combines the strengths of CT with those of PET and improves the diagnostic accuracy through better anatomic localization and characterization of lesions. A known drawback of bone scintigraphy is the high false positive rate given the prevalence of degenerative and traumatic skeletal disease in the general population. |
| **Final Recommendation**: **2A**—In adults with lung cancer where bone metastasis is suspected, PET-CT is recommended. If PET-CT is unavailable, bone scintigraphy can be used. |

**PICO #6:** In adults with non-small cell lung cancer (NSCLC), when is imaging to identify brain metastases warranted for optimal patient management?

| SEMPI Grading QOE – Table 2A.6a – Summary of Findings | | | | | | |
|---|---|---|---|---|---|---|
| **PICO #6:** In adults with non-small cell lung cancer (NSCLC), when is imaging to identify brain metastases warranted for optimal patient management? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Zhuge et al., 2019<br>Preoperative brain MRI for clinical stage IA lung cancer: is routine scanning rational? | Retrospective single center<br><br>NSCLC = Non-small cell lung cancer | N=3392 with NSCLC<br><br>170 identified with brain metastases pre-operatively | Brain MR with contrast performed in all patients. No comparator | Clinical stage and incidence of brain metastases:<br>IA – 11 (0.7%) - Reference<br>IB - 5 (2.0%) OR = 6.96<br>II - 19 (3.6%) OR = 7.91<br>III - 68 (8.8%) OR = 18.29<br>IV - 67 (28.3%) OR = 56.65<br>($p < 0.025$)<br><br>149/170 (88%) with brain metastases were asymptomatic | Although the likelihood of brain metastases significantly increases with advancing stage of non-small cell lung cancer, it is found in Stage IA and B. The presence of brain metastases does **not** correlate with symptomatology. | Low |
| Ando et al., 2018<br>Early stage non-small cell lung cancer patients need brain imaging regardless of symptoms | Retrospective<br><br>Non-small cell lung cancer (NSCLC) | N=124, brain metastases in 46 | Brain imaging preoperatively in NSCLC--no comparator (MR in all but 2—CT) | Clinical stage and incidence of brain metastases:<br>T1 – 10/46 (22%)<br>T2 – 16/46 (35%)<br>T3 - 6/46 (13%)<br>T4 - 14/46 (30%)<br>Asymptomatic with brain metastases:<br>Overall – 29/46 (63%)<br>Stage T1 – 5/29 (17%)<br>Stage T2 – 9/29 (31%) | The likelihood of brain metastases does not correlate with advancing stage of non-small cell lung cancer (NSCLC) and occurs at every stage regardless of symptomatology. Brain imaging is warranted in all NSCLC patients prior to initial surgical intervention. | Low |
| O'Dowd et al., 2014<br>Brain metastases following radical surgical treatment of non-small cell lung cancer: is preoperative brain imaging important? | Retrospective single center<br><br>Patients had curative-intent surgery for non-small | N=646, all had pre-op PET-CT (vertex to mid-thigh) confirmation of NO distant metastases | NA | 6.3% (41/646) developed brain metastases post-op—all asymptomatic preoperatively<br><br>Clinical stage and incidence of brain metastases post-op:<br>1A - 6 (14.6%) | Earlier detection of brain metastases with pre-operative magnetic resonance (MR) imaging in **all** patients with non-small cell lung cancer could provide | Low |

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| | cell lung cancer (NSCLC) having been screened with PET-CT from vertex to mid-thigh and had no known metastases | from 2006-2011<br><br>Identified those who developed brain metastases from records over 12 months | | 1B - 10 (24.4%)<br>IIA - 11 (26.8%)<br>IIB - 3 (7.3%)<br>IIIA – 10 (24.4%)<br>IIIB – 1 (2.44%)<br><br>71% (estimate based on doubling time of brain lesion) would have been found with enhanced MR imaging pre-op avoiding surgery or providing an opportunity to treat oligometastatic disease | more accurate staging and thus reduce morbidity and mortality | |
| Initial QOE Score Across Studies for PICO #6: **Low (3)** | | | | | | |

| SEMPI Grading QOE – Table 2A.6b – Risk of Bias | | |
|---|---|---|
| **PICO #6:** In adults with non-small cell lung cancer (NSCLC), when is imaging to identify brain metastases warranted for optimal patient management? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score Across studies for PICO: **LOW** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of bias | Serious | Zhuge: Retrospective, MR not "standard" imaging for staging<br>Ando: Retrospective, unclear use of historical cohort, CT also used<br>O'Dowd: Retrospective, no comparator (hypothetical), reliance on doubling time of brain lesion |
| Inconsistency | Not Serious | |
| Indirectness | Not Serious | |
| Imprecision | Not Serious | |
| **Positive Bias** | | |
| Strength of association | Low | Histopathologic confirmation |
| Other Considerations | No | |
| **Overall Effect of Bias on Initial QOE Grade: No Change** | | |
| Final QOE Grade for Outcome Across Studies: **LOW** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

## SEMPI Grading QOE – Table 2A.6c – Evidence to Recommendations

**PICO #6:** In adults with non-small cell lung cancer (NSCLC), when is imaging to identify brain metastases warranted for optimal patient management?

### SEMPI Quality of Evidence (QOE) & Recommendation Strength

| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
|---|---|---|---|---|
| Zhuge et al., 2019<br>Preoperative brain MRI for clinical stage IA lung cancer: is routine scanning rational? | The likelihood of brain metastases, as seen on magnetic resonance (MR) imaging, increases with advancing stage of non-small cell lung cancer (NSCLC) | Low | Low (3) | Consensus (B) |
| Ando et al., 2018<br>Early stage non-small cell lung cancer patients need brain imaging regardless of symptoms | The likelihood of brain metastases, as seen on brain imaging, increases with positive epithelial growth factor receptor (EGFR), advancing stage of non-small cell lung cancer (NSCLC) and occurs at every stage regardless of symptomatology. Routine brain imaging is warranted in all these cases. | Low | | |
| O'Dowd et al., 2014<br>Brain metastases following radical surgical treatment of non-small cell lung cancer: is preoperative brain imaging important? | Early detection of brain metastases with pre-operative MR could lead to earlier treatment thus reducing the morbidity and mortality. It could also change treatment decisions to avoid unneeded surgery and start palliative care sooner. | Low | | |

**Recommendation Rating: 3B**— Consensus recommendation for the intervention based on low quality evidence that is insufficient to support imaging all NSCLC patients versus various patient subsets

**Justification:** Risk of bias insufficient to downgrade QOE given histopathology/radiologic confirmation

**Rating Definitions**:

**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**

**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus

**Conclusion:** Although recent literature suggests that brain metastases are more common in early stages (e.g. IA and B) or in asymptomatic patients with non-small cell lung cancer (NSCLC) (Hudson et al., 2017; Lim & Um, 2018), definitive literature is lacking at this time to support brain imaging in all NSCLC populations (stage I/II). Magnetic resonance (MR) of the brain is the imaging modality of choice for metastatic brain lesions given its ability to identify smaller defects with greater resolution compared to computed tomography (CT) imaging; nonetheless, CT imaging of the head is used simultaneously in patients undergoing CT of the chest, abdomen and pelvis for NSCLC staging.

**Final Recommendation: 3B**—In patients with stage III or higher non-small cell lung cancer (NSCLC), or in those who are symptomatic, magnetic resonance (MR) imaging of the brain without and with contrast is recommended for assessment of metastatic spread.

**PICO #7:** In adults with non-small cell lung cancer (NSCLC), who have had curative treatment, which imaging modality should be used for surveillance?

| SEMPI Grading QOE – Table 2A.7a – Summary of Findings | | | | | | |
|---|---|---|---|---|---|---|
| **PICO #7:** In adults with non-small cell lung cancer (NSCLC), who have had curative treatment, which imaging modality should be used for surveillance? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Reddy et al., 2017 Influence of Surveillance PET/CT on Detection of Early Recurrence After Definitive Radiation in Stage III Non-small-cell Lung Cancer | Retrospective | N=200 patients (stage III NSCLC) | PET-CT vs CT | CT vs PET:<br>Event free survival-<br>21.4 vs 29.4 months (p=0.59).<br>Overall survival-<br>41.2 vs 41.3 months (p = 0.59).<br>Local recurrence-free survival (p=0.92)<br>Distant metastases-free survival I will (p=0.30) | Routine PET-CT surveillance confers no additional benefit over CT alone in detecting local or distant recurrence in non-small cell lung cancer patients who have had curative treatment | Moderate |
| Backhus et al., 2016 Imaging surveillance and survival for surgically resected non-small-cell lung cancer | Retrospective | Patients > 65-year-old with stage I or II NSCLC that has been surgically treated – 18406 | Post-operative CT surveillance vs XR, PET-CT, and clinical surveillance during the early post-operative period 4 – 8 months. | Early CT was associated with an overall survival benefit (15% reduced risk of death) in patients with stage I NSCLC (HR: 0.85, 95% CI 0.74 – 0.98)<br><br>PET-CT and XR had the lowest survival rate among the cohort (53% and 57.9% respectively).<br><br>The overall 5 yrs. survival rate was not statistically significant between CT and clinical surveillance groups (P = 0.110) | Early post-operative CT surveillance may provide survival benefit for stage I non-small cell lung cancer (NSCLC) | Moderate |
| Hanna et al., 2014 Minimal-dose computed tomography is superior to chest x-ray for the follow-up and treatment of patients with resected lung cancer | Prospective, paired comparative study for detection of recurrence or new lung cancer | NSCLS adult patients after curative-intent treatment, single site, 2007-2012 N=271 patients, | Minimal –dose CT (MnDCT) and chest XR performed on all patients at 3,6,12,18,24,36, 48, and 60 months following initial curative | Sensitivity=94.2% MnDCT versus 21.2% for chest XR, p<0.0001.<br>Negative predictive value=99.7 for MnDCT vs 96.2% for chest XR, p=0.007. However, MnDCT had a specificity of 86% and PPV of 25.1% versus a specificity of 99.9% and PPV of 91.7% for CXR (p<0.0001).<br>Of the 63 patients (23%) with recurrence or new lung cancer, 49 (78%) were asymptomatic and 37/49 (75%) underwent | Minimal-dose CT imaging is superior to chest x-ray for the detection of recurrent or new lung cancer. | Moderate |

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| | | 1137 paired CT and MnDCT | | curative-intent treatment with median survival= 69 months vs 12 of 49 with palliative care, median survival of 25 months (p<0.0001) | | |
| Crabtree et al., 2015 Does the method of radiologic surveillance affect survival after resection of stage I NSCLC? | Retrospective Single Center | All patients undergoing curative resection for stage I NSCLC from 2000-2013 N=554 patients, 232=CT versus 322=XR | CT versus chest XR done "at discretion" of treating physician. Time to recurrence and survival analyzed | Among patients who developed recurrence/second malignancy, 49% in the CT group were asymptomatic versus 19% in the XR group (p < 0.001). Time to diagnosis of second malignancy/recurrence was 1.93 years for CT and 2.6 years for XR, p=0.046. | Surveillance CT imaging can result in earlier detection of recurrent/new malignancy compared to chest x-ray in Stage I non-small cell lung cancer (NSCLC) | Low |
| Lamont et al., 2002 Systematic postoperative radiology follow-up in patients with non-small cell lung cancer for detecting second primary lung cancer in Stage IA | Retrospective Observational | Patients with NSCLC followed post initial curative treatment for Stage IA N=124 | CT performed annually with chest XR done q 4mos x 2 years then q 6mos x 3 years | Median diameter of resected second tumors=14mm versus 26.5mm detected by chest XR, p<0.001 | CT imaging detects second primary lung cancer at an earlier stage than chest x-ray in non-small cell lung cancer patients who have had curative treatment. | Moderate |
| Initial QOE Score Across Studies for PICO #7: **Moderate (2)** | | | | | | |

| SEMPI Grading QOE – Table 2A.7b – Risk of Bias | | |
|---|---|---|
| **PICO #7:** In adults with non-small cell lung cancer (NSCLC), who have had definitive treatment, should CT imaging be performed for surveillance compared to XR for optimal patient management? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score Across Studies for PICO: **MODERATE** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of Bias | Serious | Lack of prospective randomized studies |
| Inconsistency | Serious | CT protocols different |
| Indirectness | Not Serious | |
| Imprecision | Not Serious | |
| **Positive Bias** | | |
| Strength of Association | Low | |
| Other Considerations | No | |
| **Overall Effect of Bias on Initial QOE Grade: Downgraded to LOW** | | |
| Final QOE Grade for Outcome Across Studies: **LOW** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

## SEMPI Grading QOE – Table 2A.7c – Evidence to Recommendations

**PICO #7:** In adults with non-small cell lung cancer (NSCLC), who have had curative treatment, which imaging modality should be used for surveillance?

### SEMPI Quality of Evidence (QOE) & Recommendation Strength

| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
|---|---|---|---|---|
| Reddy et al., 2017 Influence of Surveillance PET/CT on Detection of Early Recurrence After Definitive Radiation in Stage III Non-small-cell Lung Cancer | Routine PET-CT surveillance confers no additional benefit over CT alone in detecting local or distant recurrence in non-small cell lung cancer patients who have had curative treatment | Moderate | Moderate (2) | Consensus (B) |
| Backhus et al., 2016 Imaging surveillance and survival for surgically resected non-small-cell lung cancer | Early post-operative CT surveillance may provide survival benefit for stage I non-small cell lung cancer (NSCLC) | Moderate | | |
| Hanna et al., 2014 Minimal-dose computed tomography is superior to chest x-ray for the follow-up and treatment of patients with resected lung cancer | Minimal-dose CT imaging is superior to chest x-ray for the detection of recurrent or new lung cancer. | Moderate | | |
| Crabtree et al., 2015 Does the method of radiologic surveillance affect survival after resection of stage I NSCLC? | Surveillance CT imaging can result in earlier detection of recurrent/new malignancy compared to chest x-ray in Stage I non-small cell lung cancer (NSCLC) | Low | | |
| Lamont et al., 2002 Systematic postoperative radiology follow-up in patients with non-small cell lung cancer for detecting second primary lung cancer in Stage IA | CT imaging detects second primary lung cancer at an earlier stage than chest x-ray in non-small cell lung cancer patients who have had curative treatment. | Moderate | | |

**Recommendation Rating: 2B**—Consensus recommendation for the intervention based on moderate quality evidence
**Justification:** Paucity of high-quality data assessing the optimal imaging modality, interval and duration of surveillance following definitive treatment of lung cancer leads to a consensus recommendation; risk of bias insufficient to downgrade QOE.

**Rating Definitions**:

**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**
**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus

**Conclusion:** For patients who have undergone initial curative treatment for NSCLC, there is a lack of high-quality evidence to support one imaging modality over another for surveillance monitoring. Nonetheless, it is generally agreed that due to a high recurrence rate, especially within the first 2-3 years, patients who have undergone curative-intent treatment for NSCLC should have scheduled imaging as part of their follow-up to detect recurrence/ metastases and/or new primary lung cancer (Calman et al., 2011; Nguyen et al., 2018). CT imaging is known

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| to be significantly more sensitive than chest x-ray in thoracic disease detection and evidence suggests that asymptomatic recurrence detection has significantly better outcomes and improved survival than symptomatic recurrence. The consensus from published guidelines (NCCN, ESMO, AATS and AACP) is to do a CT with and without contrast every 6 months for the first 2-3 years. In recent years, literature evaluating the efficacy of PET-CT for surveillance in NSCLC is increasing (Sheikhbahaei et al., 2017; Reddy et al., 2017) but the evidence regarding the benefits is inconclusive and no clinical advantage (survival outcomes) of PET-CT over CT surveillance has been documented (Reddy et al., 2017). |
| **Final Recommendation**: **2B**—In adults with non-small cell lung cancer (NSCLC) who have had curative treatment, chest CT without and with contrast is recommended for surveillance imaging. |

**PICO #8:** In adults with limited stage small cell lung cancer (SCLC), who have had definitive treatment, should CT imaging be performed as part of surveillance monitoring for optimal patient management?

| SEMPI Grading QOE – Table 2A.8a – Summary of Findings | | | | | | |
|---|---|---|---|---|---|---|
| **PICO #8:** In adults with limited stage small cell lung cancer (SCLC), who have had definitive treatment, should CT imaging be performed as part of surveillance monitoring for optimal patient management? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Kono et al., 2017 Incidence of Second Malignancy after Successful Treatment of Limited-Stage Small–Cell Lung Cancer and Its Effects on Survival | Retrospective study | N=541 | Patients with SCLC and metachronous second malignancy (MSM) vs. patients with SCLC and no other malignancy. All after successful treatment of LSCLC | 10-year survival rates:<br>-Patients who developed MSM - 61.9% (95%CI :30%-83%)<br>-Did not develop secondary malignancy – 29.9% (95% CI: 21.5%-38.6%) | Surveillance monitoring with CT chest/abdomen can identify a second malignancy in patients with SCLC who have had definitive treatment | Low |
| Früh et al., 2013 Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up | Clinical Practice Guidelines from European Society of Medical Oncology (ESMO); also endorsed by Japanese Society of Medical Oncology (JSMO) | N/A | Updated guidelines for diagnosis, treatment and follow-up of patients with small cell lung cancer (SCLC) | Two to three-monthly CT scans are recommended in patients with metastatic disease potentially qualifying for further treatments<br><br>3 to 6 monthly CT scans for 2 years with lengthening of intervals thereafter are recommended for patients with non-metastatic disease who have received potentially curative treatment | Scheduled CT imaging is included in surveillance of treated small cell lung cancer (SCLC) patients. This represents a clinical practice standard of care and is not based on clinical trial data | Low |
| Colt et al., 2013 Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians | Updated guidelines | N/A | Update clinical practice guidelines | N/A | Scheduled CT imaging is included in surveillance of treated small cell lung cancer (SCLC) patients. This represents a clinical practice standard of care and is not based on clinical trial data | Low |

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| evidence-based clinical practice guidelines | | | | | | |
| Initial QOE Score Across Studies for PICO #8: **Low (3)** | | | | | | |

| SEMPI Grading QOE – Table 2A.8b – Risk of Bias | | |
|---|---|---|
| **PICO #8:** In adults with limited stage small cell lung cancer (SCLC), who have had definitive treatment, should CT imaging be performed as part of surveillance monitoring for optimal patient management? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score Across studies for PICO: **LOW** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of bias | | Not assessed, clinical practice guideline recommendations |
| Inconsistency | | Not assessed, clinical practice guideline recommendations |
| Indirectness | | Not assessed, clinical practice guideline recommendations |
| Imprecision | | Not assessed, clinical practice guideline recommendations |
| **Positive Bias** | | |
| Strength of association | | Not assessed, clinical practice guideline recommendations |
| Other Considerations | | Not assessed, clinical practice guideline recommendations |
| **Overall Effect of Bias on Initial QOE Grade: No Change** | | |
| Final QOE Grade for Outcome Across Studies: **LOW** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

## SEMPI Grading QOE – Table 2A.8c – Evidence to Recommendations

**PICO #8:** In adults with limited stage small cell lung cancer (SCLC), who have had definitive treatment, should CT imaging be performed as part of surveillance monitoring for optimal patient management?

### SEMPI Quality of Evidence (QOE) & Recommendation Strength

| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
|---|---|---|---|---|
| Kono et al., 2017 Incidence of Second Malignancy after Successful Treatment of Limited-Stage Small–Cell Lung Cancer and Its Effects on Survival | Surveillance monitoring with CT chest/abdomen can identify a second malignancy in patients with SCLC who have had definitive treatment | Low | Low (3) | Consensus (B) |
| Früh et al., 2013 Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up | Scheduled CT imaging is included in surveillance of treated small cell lung cancer (SCLC) patients. This represents a clinical practice standard of care and is not based on clinical trial data | Low | | |
| Colt et al., 2013 Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines | Scheduled CT imaging is included in surveillance of treated small cell lung cancer (SCLC) patients. This represents a clinical practice standard of care and is not based on clinical trial data | Low | | |

**Recommendation Rating: 3B**—Recommendation from panel member consensus for the intervention based on low quality evidence
**Justification:** Risk of bias insufficient to downgrade QOE.

**Rating Definitions**:

**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**

**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus

**Conclusion:** At the present time there is not enough clinical trial evidence to support a specific imaging modality for surveillance in patients who have had definitive treatment for limited stage small cell lung cancer (SCLC). Nonetheless, it is currently standard clinical practice to perform a CT, without and with contrast, of the chest, abdomen and pelvis at scheduled intervals following initial treatment.

**Final Recommendation: 3B**— In adults with limited small cell lung cancer (SCLC), who have had definitive treatment, CT of the chest, abdomen and pelvis without and with contrast is recommended as a part of surveillance imaging.

**PICO #9:** In which adult populations is lung cancer screening indicated and which imaging modality is preferred for optimal management/assessment?

| SEMPI Grading QOE – Table 2A.9a – Summary of Findings | | | | | | |
|---|---|---|---|---|---|---|
| **PICO #9:** In which adult populations is lung cancer screening indicated and which imaging modality is preferred for optimal management/assessment? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Smith et al., 2018 Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening | Literature review and update of 2017 American Cancer Society Guideline on Lung Cancer Screening with Low Dose CT (LDCT) imaging | **Age**: 55-74 years **Smoking Hx:** Active or former smoker with a 30-pack-yr history or quit within 15 years **Active Smoker:** If active smoker, vigorously urged to enter a smoking cessation program **General health exclusions:** -Metallic implant or device in the chest/back -Requirement for home oxygen use -Prior hx of lung cancer | N/A | Clarification added in 2017: Annual screening for lung cancer with low dose CT (LDCT) is recommended in adults aged 55-74 in relatively good health with a 30 pack-year smoking history and either currently smoke or have quit within the past 15 years-- AND have received evidence-based smoking cessation counseling if current smoker<br><br>AND have undergone a process of informed/shared decision-making that includes information about the potential benefits, limitations, and harm of screening with LDCT (e.g. high false positive result rate, rare major complication resulting from false-positive results)<br><br>AND have access to a high-volume, high-quality lung cancer screening and treatment center | Annual lung cancer screening with low dose CT imaging is recommended in current or former smokers, between 55 and 74 years of age, who meet additional specific criteria related to smoking cessation, informed/shared decision-making, and access to high-quality lung cancer centers | Low |
| Jemal & Fedewa, 2017 Lung cancer screening with low-dose computed tomography in the United States—2010 to 2015 | Data review from National Health Interview Survey (NHIS) from 2010-2015 | N=2347 NHIS survey respondents<br><br>Determine if annual lung CA screening with LDCT increased | NA<br><br>USPSTF=US Protective Services Task Force | 2010 NHIS survey results=3.3% of eligible patients screened with LDCT<br><br>2015 NHIS survey results=3.9% of eligible patients screened with LDCT (p=0.6)<br><br>Of 6.8 million smokers eligible for LDCT screening, 262,700 received it | Annual low-dose CT (LDCT) screening among heavy current and former smokers remains low despite the 2013 US Protective Services Task Force guidance which | Moderate |

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|---|---|---|---|---|---|---|
| | Determine percent of eligible patients undergoing Low Dose CT screening for Lung CA | following 2013 guidance by USPSTF for high-risk populations | Multivariable prevalence ratios of LDCT estimated using predicted margins | Greater than half of those eligible-uninsured or Medicaid insured<br><br>LDCT screening (1230/2167)<br>2013 guidance screen lung CA: annual LDCT of chest in those 55-80yrs of age with 30 pack year smoking history, active smokers or quit within past 15 years | demonstrates lower mortality when screening is performed | |
| National Lung Screening Trial Research Team et al., 2013<br>Results of initial low dose computed tomographic screening for lung cancer | Prospective, randomized trial<br><br>Multicenter (33) from 2002-2004<br><br>Follow-up of National Lung Screening Trial (NLST) in 2011 | N=53,439 asymptomatic adults, 55-74 years of age, 30 pack-year smoking history<br><br>These are results of initial screening | Low dose CT (LDCT) vs Chest XR (XR)<br><br>Nodules and other suspicious findings deemed "positive" | 26,309 participants (98.5%) and 26,035 (97.4%) underwent screening<br>7191 (27.3%)-LDCT and 2387 (9.2%)-XR had positive screening results<br>6369 (90.4%)-LDCT and 2176 (92.7%)-XR had at least one follow-up diagnostic procedure, including imaging and surgery Lung CA diagnosed in 292 (1.1%)-LDCT versus 190 (0.7%)-XR group<br>Sensitivity/Specificity:<br>LDCT=93.8%/73.4% XR=73.5%/91.3% | The NLST initial screening results are consistent with the existing literature on screening by means of low-dose CT versus chest radiography, suggesting that a reduction in mortality from lung cancer is achievable at U.S. screening centers that have staff experienced in chest CT interpretation | Moderate |
| National Lung Screening Trial Research Team et al., 2011<br>Reduced lung-cancer mortality with low-dose computed tomographic screening | Prospective, randomized study<br><br>National Lung Screening Trial (NLST) assess whether low-dose CT (LDCT) can reduce lung CA mortality<br><br>(enrollment 2002-2004) | N=53,454 asymptomatic adults, 55-74 yrs of age, 30 pack-yr smoking history<br><br>3 annual screening visits with either LDCT or chest XR<br><br># Lung CA Dx and # deaths from lung CA | LDCT, chest XR<br><br>Results based on events occurring through 2009 | 90% adherence rate to screening<br>Positive screenings: 24%-LDCT vs 7%-XR<br>False Positive screenings:<br>96%-LDCT and 95%-XR<br>Incidence of lung CA:<br>645 cases/100,000 person-years (1060 cancers)-LDCT<br>vs<br>572 cases/100,000 person-years (941 cancers)-XR<br>(rate ratio, 1.13; 95% CI, 1.03 to 1.23)<br>**Lung CA deaths: 247/100,000 person-years in LDCT group vs 309/100,000 person-years in XR group, representing a mortality relative reduction rate of 20% with LDCT screening (95% CI, 6.8 to 26.7; P=0.004)** | Lung cancer screening with low-dose CT (LDCT) reduces mortality from lung cancer compared to chest radiography (XR) screening | High |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | Complication rate of diagnostic procedure for a positive screening test didn't differ: 1.4% LDCT vs 1.6% XR | | |
| Initial QOE Score Across Studies for PICO #9: **Moderate (2)** | | | | | | |

| SEMPI Grading QOE – Table 2A.9b – Risk of Bias | | |
|---|---|---|
| **PICO #9:** In which adult populations is lung cancer screening indicated and which imaging modality is preferred for optimal management/assessment? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score Across Studies for PICO: **MODERATE** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of Bias | Serious | Survey date reliance, review article overreliance, recall bias, prevalence ratios estimated (prediction margins), vintage effect of equipment, lower disease prevalence and lower surgical complication rates in study population vs general population, centers of excellence used for guideline development, availability of LDCT vs XR |
| Inconsistency | Not Serious | |
| Indirectness | Not Serious | |
| Imprecision | Not Serious | |
| **Positive Bias** | | |
| Strength of Association | Low | |
| Other Considerations | Yes | Histopathology confirmation |
| **Overall Effect of Bias on Initial QOE Grade: No change** | | |
| Final QOE Grade for Outcome Across Studies: **MODERATE** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

## SEMPI Grading QOE – Table 2A.9c – Evidence to Recommendations

**PICO #9:** In which adult populations is lung cancer screening indicated and which imaging modality is preferred for optimal management/assessment?

### SEMPI Quality of Evidence (QOE) & Recommendation Strength

| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
|---|---|---|---|---|
| Smith et al., 2018<br>Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening | Annual lung cancer screening with low dose CT imaging is recommended in current or former smokers, between 55 and 74 years of age, who meet additional specific criteria related to smoking cessation, informed/shared decision-making, and access to high-quality, lung cancer centers | Low | Moderate (2) | Strong (A) |
| Jemal & Fedewa, 2017<br>Lung cancer screening with low-dose computed tomography in the United States—2010 to 2015 | Annual low-dose CT (LDCT) screening among heavy current and former smokers remains low despite the 2013 US Protective Services Task Force guidance which demonstrates lower mortality when LDCT screening is performed | Moderate | | |
| National Lung Screening Trial Research Team et al., 2013<br>Results of initial low-dose computed tomographic screening for lung cancer | The NLST initial screening results are consistent with the existing literature on screening by means of low-dose CT versus chest radiography, suggesting that a reduction in mortality from lung cancer is achievable at U.S. screening centers that have staff experienced in chest CT interpretation | Moderate | | |
| National Lung Screening Trial Research Team et al., 2011<br>Reduced lung-cancer mortality with low-dose computed tomographic screening | Lung cancer screening with low-dose CT (LDCT) reduces mortality from lung cancer compared to chest radiography (XR) screening | High | | |

**Recommendation Rating: 2A**—Strong recommendation for the intervention based on moderate quality evidence
**Justification:** Inadequate risk of bias to downgrade the literature reviewed given histopathology confirmation and guideline comparisons.

**Rating Definitions**:

**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**

**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus

| |
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| **Conclusion:** Several large randomized clinical trials (NLST, NELSON and ELCAP) have shown consistent reduction in lung cancer deaths with CT screening (De Koninget al., 2018; Moyer, 2014). Based on the NLST data, USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. Additionally, patients should have a conversation regarding risks/benefits of such screening as well as access to imaging centers. The American Cancer Society also has determined that there is adequate evidence to support LDCT for lung cancer screening for asymptomatic beneficiaries aged 55-74 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years (Smith et al., 2018). |
| **Final Recommendation**: **2A**—In adults aged 55-80 years with a 30 pack-year smoking history and who currently smoke or have quit within the past 15 years, annual lung cancer screening with unenhanced low dose CT (LDCT) is recommended. |

**PICO #10:** In adults found to have a Solitary Pulmonary Nodule(s) (SPNs), should PET-CT or CT imaging be performed to differentiate between benign and malignant lesions?

| SEMPI Grading QOE – Table 2A.10a – Summary of Findings | | | | | | |
|---|---|---|---|---|---|---|
| **PICO #10:** In adults found to have a Solitary Pulmonary Nodule(s) (SPNs), should PET-CT or CT be performed to differentiate between benign and malignant lesions? | | | | | | |
| Author/Year/Title | Design | Population | Intervention Vs Comparator | Results | Conclusion Summary | SEMPI QOE Rating |
| Jia et al., 2019 Comparing the diagnostic value of $^{18}$F-FDG-PET/CT versus CT for differentiating benign and malignant solitary pulmonary nodules: a meta-analysis | Meta-analysis | N=39 studies included (16 studies for CT (13 with contrast enhanced CT) and 23 for PET-CT)) | PET-CT vs CT | **Pooled estimates-**<br>**CT:**<br>Sensitivity: 0.94 (95% CI: 0.87-0.97]<br>Specificity: 0.73 (95% CI: 0.64-0.80)<br>Positive Likelihood Ratio: 3.45 (95% CI: 2.60-4.58)<br>Negative Likelihood Ratio: 0.09 (95% CI: 0.04-0.17)<br>Diagnostic Odds Ratio: 32.01 (95% CI: 15.10-67.86)<br>Area Under Curve: 0.89 (95% CI: 0.86-0.91)<br><br>**PET-CT:**<br>Sensitivity: 0.89 (95% CI: 0.85-0.92),<br>Specificity: 0.78 (95% CI: 0.66-0.86),<br>Positive likelihood Ratio: 3.97 (95% CI: 2.57-6.13)<br>Negative likelihood Ratio: 0.15 (95% CI: 0.10-0.20)<br>Diagnostic Odds Ratio: 24.04 (95% CI: 12.71-45.48)<br>Area Under Curve: 0.91 (95% CI: 0.89-0.94)<br>No significant differences | CT and PET- CT imaging have comparable diagnostic accuracy for evaluating Solitary Pulmonary Nodules (SPN's) | Moderate |

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|---|---|---|---|---|---|---|
| Liu et al., 2017<br>Radiologic features of small pulmonary nodules and lung cancer risk in the National Lung Screening Trial: a nested case-control study | Nested Case-Control study<br><br>Evaluate radiologic features of solitary pulmonary nodules (SPN) from baseline Low dose CT screening deemed "negative" by National Lung Screening Trial (NLST) criteria in patients later diagnosed with lung cancer at either 1st or 2nd follow-up screen | N=73 incident cases of lung cancer in those with initial "negative" LDCT and 157 control subjects who had 3 consecutive negative screening studies<br><br>Multivariable logistic regression used to assess association between radiologic features and lung cancer risk | N/A<br><br>LDCT=Low dose CT<br><br>2 radiologists | 5 LDCT features (OR) that increase lung cancer risk include:<br>Total emphysema score :(1.71)<br>Attachment to vessel: (2.41)<br>Nodule location: (3.25)<br>Border definition: (7.56)<br>Concavity of nodule: (2.58)<br>When adjusted for demographic covariates, the final model yields:<br>AUC=0.93<br>Specificity=92%<br>Sensitivity=74% | Five radiographic findings can be scored to identify those patients with small pulmonary nodules who are at increased risk for lung cancer thus reducing false negative low-dose CT screening results. | Low |
| Gould et al., 2013<br>Evaluation of individuals with pulmonary nodules: When is it lung cancer? Diagnosis and management of lunch cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines | Literature review | N/A | N/A | Estimated probability of malignancy should be part of initial evaluation of SPNs. No additional studies are required for SPNs that have a typically benign pattern on CT (intralesional fat, popcorn, laminate, diffuse, and central calcifications). An individual with an indeterminate nodule on chest XR should have a CT of the chest performed to characterize the nodule<br><br>Stable SPNs for > 2 years, no additional diagnostic follow-up is required | In the individual with an indeterminate nodule that is identified by chest radiography, CT of the chest should be performed (preferably with thin sections through the nodule) to help characterize the nodule | Low |
| Patel et al., 2013<br>A Practical Algorithmic Approach to the Diagnosis and | Evidence-based Guideline | N/A | N/A | Initial imaging of a SPN should be thin section CT. If the SPN lacks identifying characteristics of a benign nodule further management is based on the | Indeterminant Solitary Pulmonary Nodules (SPNs) should have probability of malignancy performed. | Low |

| | | | | | | |
|---|---|---|---|---|---|---|
| Management of Solitary Pulmonary Nodules Part 1: Radiologic Characteristics and Imaging Modalities | | | | size of nodule and whether the SPN is solid or subsolid. | Management is determined by malignant probability, nodule size, and nodule density-solid vs subsolid. Intermediate risk SPNs should have PET or PET-CT imaging. High probability SPN should have biopsy or resection. | |
| Harders et al., 2011 High resolution spiral CT for determining the malignant potential of solitary pulmonary nodules: refining and testing the test | Follow-up Study | 213 patients | High resolution spiral CT | Malignant risk categories (MRC's) ($p < 0.001$), calcification patterns ($p = 0.003$), and pleural retraction ($p < 0.001$) were all statistically significantly associated to malignancy Reproducibility was moderate to substantial Sensitivity, specificity, and overall diagnostic accuracy of HRCT were 98%, 23% and 87%, respectively Reproducibility was substantial. | Statistically significant associations between Solitary Pulmonary Nodule Malignant risk categories, calcification patterns, pleural retraction and malignancy were found on high resolution CT (HRCT) yielding a very high sensitivity | Low |
| Kim et al., 2007 Accuracy of PET/CT in Characterization of Solitary Pulmonary Lesions | Retrospective | 32 patients referred for SPN evaluation with PET/CT | Comparison of each component of the study, CT, PET and PET-CT separately for sensitivity and specificity. | CT and PET/CT are similarly sensitive (93 vs 97 %) in characterizing nodules. PET/CT is more specific (85 %) than CT (31%). The sensitivity of PET alone is less than either (69 %) but the specificity of PET is equal to PET/CT. | PET-CT has a high accuracy for determining the nature of Solitary Pulmonary Nodules. Identification of malignancy is reduced for small and/or lesions with low uptake. | Low |
| Yi et al., 2006 Tissue characterization of solitary pulmonary nodule: comparative study between helical dynamic CT and integrated PET/CT | Retrospective | 119 Patients of 330 with SPN who were evaluated with both HDCT and PET/CT. No comment on solid vs ground glass SPN. | HDCT vs PET/CT (Both studies completed on all patients) | "The sensitivity, specificity, and accuracy for malignancy on HDCT were 81% (64/79 nodules), 93% (37/40), and 85% (101/119), respectively, whereas those on integrated PET/CT were 96% (76/79), 88% (35/40), and 93% (111/119), respectively (*P* = 0.008, 0.727, and 0.011, respectively)." Sensitivity for malignant SPN by PET/CT was improved by mediastinal evidence of malignancy on PET. | Overall PET-CT performs better than helical dynamic CT in evaluating Solitary Pulmonary Nodules for malignancy. | Moderate |
| Initial QOE Score Across Studies for PICO #10: **Low (3)** | | | | | | |

| SEMPI Grading QOE – Table 2A.10b – Risk of Bias | | |
|---|---|---|
| **PICO #10:** In adults found to have a Solitary Pulmonary Nodule(s) (SPNs), should PET-CT or CT be performed to differentiate between benign and malignant lesions? | | |
| Evaluate Outcome for Risk of Bias Across Studies | | |
| Initial QOE Score Across Studies for PICO: **LOW** | | |
| **Criteria** | **Assessment** | **Reason for Assessment** |
| **Negative Bias** | | |
| Risk of Bias | Serious | Lack of prospective studies comparing CT to PET-CT. All retrospective studies (including the literature in metanalysis). |
| Inconsistency | Not Serious | |
| Indirectness | Not Serious | |
| Imprecision | Not Serious | |
| **Positive Bias** | | |
| Strength of Association | Moderate | Histopathological/biopsy confirmation |
| Other Considerations | No | |
| **Overall Effect of Bias on Initial QOE Grade: No change** | | |
| Final QOE Grade for Outcome Across Studies: **LOW** | | |
| **High** – Very confident the true effect lies close to that of the estimate of the effect<br>**Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)<br>**Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)<br>**Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect) | | |

| SEMPI Grading QOE – Table 2A.10c – Evidence to Recommendations | | | | |
|---|---|---|---|---|
| **PICO #10:** In adults found to have a Solitary Pulmonary Nodule(s) (SPNs), should PET-CT or CT be performed to differentiate between benign and malignant lesions? | | | | |
| **SEMPI Quality of Evidence (QOE) & Recommendation Strength** | | | | |
| Author/Year/Title | Highlights | SEMPI QOE Rating | Final QOE Category | Recommendation Strength |
| Jia et al., 2019<br>Comparing the diagnostic value of $^{18}$F-FDG-PET/CT versus CT for differentiating benign and malignant solitary pulmonary nodules: a meta-analysis | CT and PET- CT imaging have comparable diagnostic accuracy for evaluating Solitary Pulmonary Nodules (SPN's) | Moderate | Low (3) | Strong (A) |
| Liu et al., 2017<br>Radiologic features of small pulmonary nodules and lung cancer risk in the National Lung Screening Trial: a nested case-control study | Five radiographic findings can be scored to identify those patients with small pulmonary nodules who are at increased risk for lung cancer thus reducing false negative low-dose CT screening results. | Low | | |
| Gould et al., 2013<br>Evaluation of individuals with pulmonary nodules: When is it lung cancer? Diagnosis and management of lunch cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines | In the individual with an indeterminate nodule that is identified by chest radiography, CT of the chest should be performed (preferably with thin sections through the nodule) to help characterize the nodule | Low | | |
| Patel et al., 2013<br>A Practical Algorithmic Approach to the Diagnosis and Management of Solitary Pulmonary Nodules Part 1: Radiologic Characteristics and Imaging Modalities | Indeterminant Solitary Pulmonary Nodules (SPNs) should have probability of malignancy performed. Management is determined by malignant probability, nodule size, and nodule density-solid vs subsolid. Intermediate risk SPNs should have PET or PET-CT imaging. High probability SPN should have biopsy or resection. | Low | | |
| Harders et al., 2011<br>High resolution spiral CT for determining the malignant potential of solitary pulmonary nodules: refining and testing the test | Statistically significant associations between Solitary Pulmonary Nodule Malignant risk categories, calcification patterns, pleural retraction and malignancy were found on high resolution CT (HRCT) yielding a very high sensitivity | Low | | |

| | | | | |
|---|---|---|---|---|
| Kim et al., 2007<br>Accuracy of PET/CT in Characterization of Solitary Pulmonary Lesions | PET-CT has a high accuracy for determining the nature of Solitary Pulmonary Nodules. Identification of malignancy is reduced for small and/or lesions with low uptake. | Low | | |
| Yi et al., 2006<br>Tissue characterization of solitary pulmonary nodule: comparative study between helical dynamic CT and integrated PET/CT | Using chest radiography, SCT and HRCT, a precise morphological assessment of the periphery of the pulmonary lesion and the adjacent visceral pleura is necessary to distinguish MSPLs from BSPLs. In this respect SCT and HRCT are useful in differentiation of MSPLs from BSPLs | Moderate | | |
| **Recommendation Rating: 3A**—Strong recommendation for the intervention based on low quality evidence<br>**Justification:** Low quality literature due to lack of prospective studies but histopathologic confirmation of data led to keeping the evidence as low rather than downgrading it despite bias. | | | | |
| **Rating Definitions**:<br>**Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**<br>**Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus | | | | |
| **Conclusion:** Solitary pulmonary nodule(s) do not present a situation that offers an opportunity for an 'either/or' imaging recommendation given a paucity of high quality prospective, randomized clinical trial data. Without prior imaging for comparison, High-Resolution CT (HRCT) without contrast is the next step in management. Subsequent evaluation is dependent on: Probable risk of malignancy, Nodule size, Solid vs Nonsolid nodule. Several prediction models are available to assist in determining the probability of malignancy in an individual patient's clinical situation (Perandini et al., 2016; Soardi et al., 2017). These models can assist in management decisions including biopsy/resection or additional imaging. | | | | |
| **Final Recommendation**: **3A**—High-Resolution CT (HRCT) without contrast is recommended for initial imaging of solitary pulmonary nodule(s) (SPNs). | | | | |

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